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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,267	THOMSON, AXEL ANDREAS	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,18,19,21 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8, 18-19, 21 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after non-final rejection filed on December 10, 2007 is acknowledged. Claims 6-7, 9-17, 20, 22-23 and 27-29 have been cancelled. Claims 1-5, 8, 18-19, 21 and 24-26 are pending in this office action. Applicant's elected with traverse of GnRH agonist and prostate cancer in the reply filed on May 03, 2007. The restriction was deemed proper and made FINAL in the previous office action. Claims 1-5, 8, 18-19, 21 and 24-26 are examined in this office action.

Applicant requests withdrawal of the election of species requirement because the PTO has asserted that the specification is enabling for "ameliorating the basal cell carcinoma and suppressing the effects of testosterone in patients with glioblastoma, and regulating prostatic growth *in vitro*.." (see p. 9 or Remarks). The subject matter outside the scope of the elected species has not been considered. The subject matter as disclosed in specification has been examined for enablement purposes only. Therefore, the restriction is maintained.

Withdrawn Objections and Rejections

1. All objections and rejections not cited herein are hereby withdrawn due to Applicant's arguments or amendments.

Maintained Rejection

35 U.S.C. 112, 2nd

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites, “A method of protecting a male patient from possible adverse effects on the prostate…” The phrase in context to adverse effects on the prostate is unclear. It is unclear what are considered to be "adverse effects." For example, different patients will consider different level of symptoms as an "adverse effect" The specification has not defined what is an adverse effect.

4. Claim 1 recites the limitation “the" in "inhibition of the SHH-signaling". There is insufficient antecedent basis for this limitation in the claim.

Response to Applicant’s Arguments

5. Applicant argues that “claim 1 has been amended to indicate that the adverse effect is “on the prostate.” And this language cannot include such things as rashes, sore muscles, dry mouths, headaches, etc.” In regards to insufficient antecedent basis of “the SHH-signaling pathway”, Applicant argues that “claim 1 recites in the preamble the phrase "a treatment involving inhibition of the SHH-signaling pathway in the patient." and this language makes clear that it is the SHH-signaling pathway in the patient that is being inhibited. It is implicit that the patient possesses such a pathway and therefore, there’s no need to require modification of the claim language.”

6. Applicant’s arguments have been fully considered but have not been found persuasive because it is unclear from the claim and the specification what the adverse

effects on the prostates are. The specification has not defined or given examples of what these adverse effects on the prostate are. For example, an adverse effect on the prostate can be a prostate cancer or frequent urination to discomfort. From the claims and the specification, it is clearly not defined what these effects are. In regards to the insufficient antecedent basis, SHH-signaling pathway is first mentioned at line 2 of claim 1. Since this is the first time SHH-signaling pathway is being recited, it clearly lacks antecedent basis.

Revised and Maintained-35 U.S.C. 112, 1st

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims1-5, 8, 21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ameliorating the basal cell carcinoma and suppressing the effects of testosterone in patients with glioblastoma, and regulating prostatic growth in vitro, does not reasonably provide enablement for treatment of all cancers in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

9. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re*

Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method of treating proliferative disease (cancer) in a patient comprising inhibiting the SHH-signaling pathway by administration of cyclopamine and suppressing testosterone or its effect in the patient by administering GnRH agonist. Further, the invention is drawn to a method of protecting a patient from proliferative disease (cancer) in a patient comprising inhibiting the SHH-signaling pathway and suppressing testosterone or its effect in the patient by administering GnRH agonist. Claim 1 and the specification have not defined what possible adverse effects on the prostate are. The Examiner has interpreted this claim as protecting a male patient from prostate cancer.

(2) The state of the prior art:

In regards to "preventing prostate cancer", Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in

unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

The state of the art with respect to animal models indicates that xenograft mouse models are poor predictors of tumor behavior in humans. Van Weerden et al state that "in vivo models are essential for the study of the biological behavior of tumor tissue in its natural (organ) environment that cannot easily be mimicked in an in vitro setting. Important physiological processes that are lacking in vitro include three-dimensional structure, angiogenesis, stromal interaction influencing tumor development and tumor growth, and finally metastatic spread to other tissues" (see p. 267, right column, Discussion). Trisha Gura echoes similar sentiments in a *Science* article. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041 or p. 1 of enclosed printout, 2nd

paragraph). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041 or p. 2 or enclosed printout, 4th paragraph). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide in culture." (See page 1042 or p. 3 or printout, 7th paragraph). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

The art provide guidance as how to alleviate some symptoms of cancer, the prior art does not provide how to determine individuals who are susceptible to cancer. However, none of the prior arts provide guidance as how to determine individuals who are susceptible to proliferative diseases.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determining the patient population that is susceptible to adverse effects on the prostate when treated with SHH-signaling pathway inhibitors, and determining the male patient population that is susceptible to proliferative disease (cancer), the predictability is low. There are different types of levels of adverse effects, and the specification has not defined what these adverse effects are on the prostate. In regards to "protecting a male patient from prostate cancer", the predictability is low. In regards to "preventing a cancers", Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis). Thus, determining patient population who are susceptible to prostate cancer is unpredictable.

In regards to treating cancer, the predictability is also low. This is due to the fact that the art has recognized the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants…*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them

cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells…solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

The claim doesn't identify the male patient population, therefore, the claim implies that any male can be protected against possible adverse effects on the prostate from a treatment involving inhibition of SHH-signaling pathway. Since "possible adverse effect" has not been defined, the claim has been interpreted as protecting a male patient from prostate cancer. Claim 2 further does not identify the male patient population, therefore, the claim implies that any male can be treated for cancer. However, the Applicant has not shown who will be susceptible to cancer and adverse effect. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

Claims 1 and dependent claims 24-26 are drawn to prevention of prostate cancer by inhibiting the SHH-signaling pathway by administering GnRH agonist. Claims 2 and dependent claims 3-5, 18-19 and 21 are drawn to a method of treating cancer in a patient wherein both GnRH agonist and cyclopamine are administered to the patient in need.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to administer the compound, it is unclear as to when to administer the compound. The specification discloses that the sonic hedgehog regulates prostatic growth and epithelial differentiation (see Example 1) and the experimentation was performed on epithelial cells in a Petri dish in vitro. Furthermore, the specification discloses that male patients presenting with basal cell carcinoma is administered with leuprorelin (GnRH agonist) (3.75 mg every four weeks intramuscularly) until castrate levels of testosterone are reached (0.5 ng/ml) and then the patient is administered cyclopamine (see Example 2). Further, the specification discloses that a male patient presenting with glioblastoma is administered flutamide (250 mg three times daily per os) to suppress the effects of testosterone, and then the patient is administered an inhibitor of the SHH-signaling pathway (see Example 3). However, there are no in vivo results that indicate Examples

2 and 3, thus there are not enough guidance useful in treating a patient with prostate cancer and any other cancers.

There are not enough working examples for guidance for treating a patient with prostate cancer. The specification discloses that the sonic hedgehog regulates prostatic growth and epithelial differentiation (see Example 1) and the experimentation was performed on epithelial cells in a Petri dish in vitro. As described above, the state of the art with respect to animal models indicates that xenograft mouse models are poor predictors of tumor behavior in humans. Van Weerden et al state that "in vivo models are essential for the study of the biological behavior of tumor tissue in its natural (organ) environment that cannot easily be mimicked in an in vitro setting. Important physiological processes that are lacking in vitro include three-dimensional structure, angiogenesis, stromal interaction influencing tumor development and tumor growth, and finally metastatic spread to other tissues" (see p. 267, right column, Discussion). Trisha Gura echoes similar sentiments in a *Science* article. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041 or p. 1 of enclosed printout, 2nd paragraph). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041 or p. 2 or enclosed printout, 4th paragraph). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide in culture." (See page 1042 or p. 3 or printout, 7th paragraph). Further, the Jain article

states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

Furthermore, the claims are drawn to the treatment of all proliferative diseases (cancer excluding prostate cancer). However, the specification has only shown effectiveness towards prostate cancer, basal cell carcinoma, and glioblastoma. It is well known that the all proliferative diseases such as cancers to not have the same mechanism of development and growth. Thus one could not assume that an agent effective against one tumor would be effective against all types of tumors. Moreover, animal models set forth for cancer are not good predictors of the efficacy in humans. As indicated in the state of the art with respect to cancer animal models, models in mice don't behave like naturally occurring tumors in humans--they don't spread to other tissues. In essence, the art indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." (See Science article on p. 1 of enclosed, 2nd paragraph). The cancer animal models and cell models, although provide valuable information for delivery of therapeutics, to not correlate to human in-vivo efficacy.

Additionally, as explained above, types of proliferative diseases are vast. The Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of

normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis). The working example provided examples of basal cell carcinoma, glioblastoma (in patients) and prostatic cells in vitro. Additionally, the specification discloses that the sonic hedgehog (SHH)-signaling pathway regulates epithelial mesenchymal interactions during the development of many organs (see paragraph [0002]), it would be found in many organs in the body. Since there are vast number of proliferative diseases that would involve SHH-signaling pathway and suppressing testosterone or its effect in the patient, more guidance is necessary.

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against adverse effects on the prostate (such as prostate cancer). The specification discloses administering the compound to basal

cell carcinoma, glioblastoma and prostatic cells in vitro. Additionally, the specification discloses that the sonic hedgehog (SHH)-signaling pathway regulates epithelial mesenchymal interactions during the development of many organs (see paragraph [0002]), it would be found in many organs in the body. Since there are vast numbers of proliferative diseases that would involve SHH-signaling pathway and suppressing testosterone or its effect in the patient, there is not enough guidance in the way of a disclosure to determine the patient population in need of such protection and treatment.

There is no clear guidance as to how to determine the patient population, since not all people suffering from proliferative diseases need suppression of testosterone. Since the prior art recognizes vast number of types of cancers, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible to prostate cancer and other types of cancer, and since different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the cyclopamine and GnRH agonist would be effective in slowing the growth rate of tumors in a subject having proliferative diseases, such as cancer.

Please note that the terms “prevent” or “protect” are absolute definitions which means to stop from occurring and, thus, requires a higher standard for enablement than does

"therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)-including preventing such disorders as prostate cancer, which is clearly not recognized in the medical art as being totally preventable condition.

Response to Applicant's Arguments

10. Applicant argues that "claims 1 and 2 are restricted to male patients who are receiving treatment with an SHH-signaling pathway inhibitor, and claim 2 is restricted to cancers (other than prostate cancer)." Applicant further argues that "the patent specification provides details of the known treatments of various diseases with SHH-signaling pathways inhibitors and provides details of known SHH-signaling pathway inhibitors. Thus, there is plainly an enabling disclosure of the treatment of patients with SHH-signaling pathway inhibitors." Additionally, Applicant argues "methods of suppressing testosterone are well known in the art and the specification clearly describes ways of suppressing testosterone." Furthermore, Applicant argues that "treatments of various diseases with SHH-signaling pathway inhibitors were known in the art and treatments for suppressing testosterone were known in the art, there can be no lack of enablement in combining these previously known treatments."

11. Applicant's arguments have been fully considered, but have not been found persuasive because claim 1 is drawn to a method of protecting a male patient from

possible adverse effects on the prostate, and possible adverse effects on the prostate have not been defined anywhere in the application. Therefore, the claim has been interpreted as a method of protecting a male patient from prostate cancer. Further, the specification describes examples on in vitro and animal models. As described above, fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see Trisha Gura, page 1041 or p. 1 of enclosed printout, 2nd paragraph). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041 or p. 2 or enclosed printout, 4th paragraph). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide in culture." (See page 1042 or p. 3 or printout, 7th paragraph). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical." Therefore, there is not enough support for in vivo efficacy, and thus not enabled for in vivo use.

In regards to Applicant's argument that suppression of testosterone would regulate cancer activity, Sekine et al (Cancer Detection and Prevention, 2007, 31(2): 149-153, pp.1-9 enclosed) indicate that decreasing testosterone values showed

worsening clinical staging and worsening histological grading (see abstract). Sekine et al studied 2914 patients diagnosed with prostate cancer (between 1982 and 2002), and examined the testosterone levels. This study indicates the suppression of testosterone did not improve the clinical staging of patients suffering prostate cancer. With Applicant's theory, every testosterone suppressor should be effective in treating cancer, but as Sekine et al indicates, this is not the case. Therefore, Applicant cannot summarize that all known testosterone suppressors or suppression of testosterone would act the same way.

35 U.S.C. 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-5, 8, 18-19, 21 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh et al (US Patent No. 5,925,619) in view of Dudek et al (WO 02/30462) and Dudek et al (US patent No. 6,291,516).

The claims are drawn to a method of treating a proliferative disease in a male patient, the method comprising inhibiting the SHH-signaling pathway and suppressing testosterone or its effects in the patient.

Walsh et al teach a pharmaceutical or veterinary formulation comprising deslorelin (a potent GnRH agonist) for the treatment of prostate and breast cancer and other conditions in humans where suppression of testosterone or estradiol levels is beneficial (see abstract and column 2, lines 49-51). This reads on claims 1 and 25-26. Furthermore, the reference teaches that when the rods containing 6 mg of deslorelin were implanted into male and female dogs, and the results show that the formulation is able to suppress testosterone levels in dogs for 12 months (see column 5, lines 61-65). The reference discloses that the formulation is used for treatment of prostate and breast cancer and other diseases ad conditions where suppression of testosterone or estradiol levels is beneficial (see abstract). Since the reference discloses the same claimed disease to be treated, same active steps (suppressing testosterone), and the same claimed active agent, the method of using GnRH agonist deslorelin would inherently suppress testosterone to castrate levels. Thus, the prior art meets the limitations of claims 1 and 25-26. The differences between the reference and the instant claim are that the reference does not teach cyclopamine and a pharmaceutically acceptable carrier.

However, Dudek et al (WO 02/30462) teach compositions and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation (cancer), including tumors, by inhibiting the hedgehog pathway, with an antagonist of the hedgehog pathway, and lists 7 compounds including cyclopamine (see abstract). The reference teaches pharmaceutical preparations comprising as an active ingredient, a hedgehog antagonist or ptc agonist formulated in an amount sufficient to inhibit, in vivo, proliferation or other biological consequences of hedgehog gain-of-function (see p. 14, lines 29-30 and continued on p. 15, lines 1-2). Furthermore, the reference teaches that the subject treatments using hedgehog antagonists can be effective for both human and animal subjects (see p. 15, lines 3-4). The reference teaches that basal cell carcinomas are skin cancers. The reference teaches the expression of SHH signaling in other cancers, such as bladder, lung, colon, breast cancer, etc (see Figures 12-15 and claims 3-7). The reference teaches that a hedgehog antagonist 5E1 can inhibit hedgehog signaling in bladder cancer cells and the same methods can be used for the small molecule antagonists, such as cyclopamine. The reference also teaches the use of hedgehog antagonists to inhibit tumor formation or progression of the colon (see Example 8). Furthermore, the reference teaches that the hedgehog antagonist is administered as part of cancer treatment regimen (see claim 22).

Furthermore, Dudek et al (US Patent No. 6,291,516) teach the pharmaceutical composition comprising small molecule such as cyclopamine, can be formulated for administration with a biologically acceptable and/or sterile medium, such as water, buffered saline, polyol or suitable mixtures thereof (see column 53, lines 18-23) and

these compounds may be administered to humans and other animals for therapy by any suitable route of administration (see column 54, lines 13-15) and that pharmaceutically acceptable carriers such as vehicle, liquid or solid filler, diluent, excipient, solvent or encapsulating materials can be utilized to carry or transport the subject regulators from one organ or portion of the body to another (see column 55, liens 55-61). Furthermore, Dudek et al teach methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting a cell with a compound (cyclopamine included in Fig. 1) in an amount sufficient to control the aberrant growth state (see abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Walsh et al and Dudek et al since both teach the treatment of proliferative diseases, cancer (prostate and others) using GnRH agonist (deslorelin, Walsh) and cyclopamine (Dudek). Furthermore, Dudek et al (US Patent '516) teach that pharmaceutically acceptable carriers can be utilized to carry or transport the subject regulators from one organ or portion of the body to another. One of ordinary skill in the art would be motivated to combine, since combining the two compounds in conjunction with a pharmaceutically acceptable carrier for the treatment of the same disease would give at least an additive effect.

Furthermore, the MPEP states the following: ""It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been

individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). In the instant case, since both agents are individually taught to treat prostate, breast and other cancers, it would be obvious to form the third composition combining the two agents to be used in the treatment of prostate cancer. Therefore, there is a reasonable expectation of success to combine the two agents along with a pharmaceutically acceptable carriers, to have an additive effect once combined and to carry or transport the subject regulators from one organ or portion of the body to another, for the treatment of proliferative disease, such

as cancer (prostate, breast, basal cell carcinoma, medulloblastoma, or giloblastoma), since "[T]he idea of combining them flows logically from their having been individually taught in the prior art'.

Response to Applicant's Arguments

15. Applicant argues that “Dudek II and Dudek I, relate to regulators of the SHH-signaling pathway and their use in treating various conditions. There is no disclosure or suggestion of using regulators of the SHH-signaling pathway in conjunction with the suppression of testosterone.” Further, Applicant argues “ the invention of claims 2-8 relates to a method of treating a proliferative disease in a male patient, where the proliferative disease is cancer in which SHH-signaling plays a role in its growth and/or differentiation, and the method includes both inhibiting the SHH-signaling pathway and suppressing testosterone or its effect in the male patient. There is no suggestion in Dudek I that inhibitors of the SHH-signaling pathway cause adverse effects on the prostate when testosterone is present. Therefore, there is no motivation whatsoever in Dudek to suppress testosterone, and so the skilled person would not have considered combining Dudek I with Walsh for treating cancers within the scope of the claims." Additionally, Applicant argues that "the two steps of the invention (of claim 2) serve different purposes in the combination therapy, one to treat the proliferative disease and the other to avoid possible adverse effects on the prostate that may be caused by the treatment of the proliferative disorder.” Further, Applicant argues that “the “obvious to try” standard is inapplicable given the nature of the claimed invention. In suggesting that

both administering an inhibitor of the SHH-signaling pathway and administering a GnRH agonist were known for treatment of prostate cancer, the PTO essentially suggests that it would have been obvious to try these two known treatments to achieve an additive effect.

16. Applicant's arguments have been fully considered but have not been found persuasive because the prior arts combined teach the treatment of cancers utilizing the compounds claimed in the instant claims. Walsh et al teach pharmaceutical or veterinary formulation comprising deslorelin (GnRH agonist) for the treatment of prostate and breast cancer and other conditions in humans where suppression of testosterone or estradiol levels is beneficial. Dudek I (WO 02/40462) teach compositions and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, with antagonist of the hedgehog pathway (cyclopamine). Since the two prior arts teach compounds in treating unwanted cell proliferation, including tumors and cancers, it would have been obvious to combine the two compounds to treat the same disease or disorder, because it would at least give an additive effect.

In regards to Applicant's argument "that there is no motivation whatsoever in Dudek to suppress testosterone", motivation to combine need not be the same as the Applicant. The MPEP states the following: "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See,

e.g., *In re Kahn*, 441 F. 3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention) See MPEP 2144.

In regards to Applicant's argument that "the "obvious to try" standard is inapplicable given the nature of the claimed invention, the rejection made was under "obvious to combine" not "obvious to try". The case laws cited (*In re Kerkhoven, In re Crockett, Ex parte Quadranti and In re Geiger*) are directed towards "obvious to combine". Therefore, Applicant's arguments are moot.

New Rejection

35 U.S.C. 112, 2nd

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claim 1 recites the limitation "the prostate" in 2nd line of the claim. There is insufficient antecedent basis for this limitation in the claim. Prostate is recited for the first time in line 2 of the claim.

19. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites, "a therapeutic system for treating a patient,

the system comprising…" The phrase "therapeutic system" is unclear. It is unclear whether therapeutic system is a mechanism (as in a method) or is an intended use.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Fri, 5:30 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654